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EXAMINER

KIM, ALEXANDER D

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

|                              |                        |                     |  |
|------------------------------|------------------------|---------------------|--|
| <b>Office Action Summary</b> | <b>Application No.</b> | <b>Applicant(s)</b> |  |
|                              | 09/914,451             | HAEGGSTROM ET AL.   |  |
|                              | <b>Examiner</b>        | <b>Art Unit</b>     |  |
|                              | Alexander D. Kim       | 1656                |  |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 05 December 2007.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 60-62,68,70-72,76 and 78-86 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 60-62,68,70-72,76 and 78-86 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)          | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

## **DETAILED ACTION**

### ***Status of the Application***

#### ***Continued Examination Under 37 CFR 1.114***

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02/06/2007 has been entered.

Applicants' amendment canceling Claims 1-59, 63-67, 69, 73-75 and 77; amending Claims 60, 62 and 70; adding new Claims 78-86, in the paper of 12/05/2007 is acknowledged. Thus, Claims 60-62, 68, 70-72, 76 and 78-86 are pending in the instant office action and will be examined herein.

#### **Claim Rejections - 35 U.S.C. § 112, Second Paragraph**

2. The previous rejection of Claims 70-77 under of 35 U.S.C. 112, second paragraph, is withdrawn by virtue of Applicants' amendment.

#### **Claim Rejections - 35 U.S.C. § 112, First Paragraph**

3. Claims 60-62, 68, 70-72, 76 and 78-86 are rejected under 35 U.S.C. § 112, first paragraph, **written description**, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the

specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection was stated in the previous office action as it applied to previous Claims 60-77. In response to this rejection, applicants have canceled Claims 1-59, 63-67, 69, 73-75 and 77; amended Claims 60, 62 and 70; added new Claims 78-86; and traverse the rejection as it applies to the newly amended claims. Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons.

Applicants argue based on the teachings in Applicants' specification as well as the general knowledge available in the art at the time of filing of the instant application, which disclose the crystallizing the LTA4 hydrolase comprising the amino acid sequence of SEQ ID NO: 1 with bestatin. Applicants also argue that new independent claims 80 and 83 is sufficiently supported by the specification such that one skilled in the art would appreciate that Applicants were in possession of the claimed invention at the time of filing because the Applicants disclose sufficiently defined the structure and functional relationship, wherein said structure is described in terms of the percent identity to a specifically disclosed amino acid sequence and the function is described in terms of the molecule as having an LTA4 hydrolase activity. Applicants further argue any variants of at least 90% identity to the amino acid sequence of SEQ ID NO: 1 is disclosed in the Tables 5-7 on pages 20 to 23. Applicants argue the disclosure of biological assays of LTA4 hydrolase activity provide the support for the written

description of LTA<sub>4</sub> variants of at least 90% identical to SEQ ID NO: 1 because the production of 10% variation from a specific amino acid is routine.

The Examiner acknowledge the Applicants disclose a method comprising a crystallization of SEQ ID NO: 1 in the presence of bestatin using the crystallization condition as set forth on page 36, lines 3-19. However, this one examples does not sufficiently describe the claimed genus method of crystallizing LTA<sub>4</sub> hydrolase (i.e., comprising SEQ ID NO: 1) under any condition. Applicants also acknowledge that crystallizing a protein is not routine and is “a major difficulties” (see page 11, middle, Remarks) and the Applicants notes that the crystallization of instant example “were only obtained when the inhibitor bestatin was present in the crystallization set-ups” (see page 36, lines 11-12). Applicants further argue, a method of crystallizing a protein having amino acid sequence at least 90% identical to SEQ ID NO: 1 is not adequately described for the reasons below. Applicants argument that the instant specification provided sufficient correlation of the structure and functional relationship, wherein said structure is described in terms of the percent identity to a specifically disclosed amino acid sequence and the function is described in terms of the molecule as having an LTA<sub>4</sub> hydrolase activity is irrelevant to the instant rejection because the instant written description rejection is about lacking correlation between the structure of LTA<sub>4</sub> protein and the function of forming LTA<sub>4</sub> protein crystal to be possessed by one skilled in the art. Applicants further argue any variants of at least 90% identity to the amino acid sequence of SEQ ID NO: 1 is disclosed in the Tables 5-7 on pages 20 to 23. However, being able to make variants having 90% identical to SEQ ID NO: 1 is irrelevant to the

instant written description rejection because the instant written description rejection is about lacking correlation between the structure of LTA<sub>4</sub> protein variant having at least 90% identity to SEQ ID NO: 1 and the function of forming the crystal of said variant protein to be possessed by one skilled in the art. Also, it may be routine to make a protein of SEQ ID NO: 1 or variant having at least 90% homology to SEQ ID NO: 1 but crystallizing a genus of protein encompassed in claims are not routine, wherein any routine method may overcome scope of enablement rejection but not instant written description rejection.

The Court of Appeals for the Federal Circuit has recently held that a “written description of an invention involving a chemical genus, like a description of a chemical species, ‘requires a precise definition, such as be structure, formula [or] chemical name,’ of the claimed subject matter sufficient to distinguish it from other materials.” *University of California v. Eli Lilly and Co.*, 1997 U.S. App. LEXIS 18221, at \*23, quoting *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these (paraphrased from *Enzo Biochemical Inc. v. Gen-Probe Inc.* (CAFC (2002) 63 USPQ2d 1609).

University of Rochester v. G.D. Searle & Co. (69 USPQ2d 1886 (2004)) specifically points to the applicability of both Lily and Enzo Biochemical to methods of using products, wherein said products lack adequate written description. While in University of Rochester v. G.D. Searle & Co. the methods were held to lack written description because not a single example of the product used in the claimed methods was described, the same analysis applies wherein the product, used in the claimed methods, must have adequate written description as noted from Enzo Biochemical (see above).

Although, a method comprising a crystallization of SEQ ID NO: 1 in the presence of bestatin (using the crystallization condition as set forth on page 36, lines 3-19) disclose a description of only one species of a protein comprising SEQ ID NO: 1 crystallization that falls within the instant genera of crystallization that is within the genera of Claims 60-62, 68, 70-72, 76 and 78-86 based on their sequence, space group symmetry, unit cell dimensions (including error), and resolution as disclosed in a crystal properties on page 36. Also, a method of crystallizing a genus of proteins with at least 90% sequence identity to SEQ ID NO: 1 as disclosed in Claims 80-86 cannot be adequately described by the instant example disclosing a species of LTA<sub>4</sub> crystal consisting of SEQ ID NO: 1. As noted above, the species of instant case does not correlate structure of protein and function of forming its crystal in the claimed genus method. Because our understanding of crystallization mechanisms are still incomplete and the factors of macromolecular structure that are involved in crystallization are poorly

understood, a method of the crystallization encompassed by the breadth of the claims is not adequately described by the method of crystallization disclosed in the specification. In general, for a species of crystallization to be adequately structurally described, the following must be adequately disclosed: a composition of the protein solution and a precipitant solution used in crystallization (exact concentrations and volumes of all molecules used in the crystallization) must be described, including (1) the protein (preferably a SEQ ID NO of all included residues) (2) any ligand added (3) the precipitant solution(s). The species of crystallization noted in Example on page 36 of the instant specification have adequately met this burden. However, the crystallization encompassed by the breadth of the claims is not adequately described because a singular chemical composition can crystallize differently based on the crystallization conditions, and the space group and unit cell dimensions of a crystal of any given chemical composition can only be determined by analyzing that crystal's X-ray diffraction (Giege et al. Crystallogensis of Biological Macromolecules: Facts and Perspectives. Acta Cryst., (1994) D50: 339-350). Therefore, the suitable condition disclosed in the specification to crystallize SEQ ID NO: 1 with bestatin cannot sufficiently describe a suitable condition of instant claimed genus method comprising a crystallization of widely varying genus proteins.

4. Claims 60-62, 68, 70-72, 76 and 78-86 are rejected under 35 U.S.C. § 112, first paragraph, **scope of enablement**, because the specification, while being enabling for a method comprising crystallization of SEQ ID NO: 1 in the presence of bestatin by the

condition described on page 36, lines 3-19, that results in a crystal having the space group P21212 and the unit cell dimensions  $a=67.59 \text{ \AA}$ ,  $b=133.51 \text{ \AA}$ ,  $c=83.40 \text{ \AA}$  and  $\alpha=\beta=\gamma=90^\circ$ ; does not reasonably provide enablement for a method comprising crystallization of SEQ ID NO: 1 (or any protein having at least 90% identity to SEQ ID NO: 1) under any crystallization condition and/or in the presence of any compound.

The rejection was stated in the previous office action as it applied to previous Claims 60-77. In response to this rejection, applicants have canceled Claims 1-59, 63-67, 69, 73-75 and 77; amended Claims 60, 62 and 70; added new Claims 78-86; and traverse the rejection as it applies to the newly amended claims. Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons.

Applicants argue one of ordinary skill in the art would be able to make and use the claimed invention (i.e., crystallizing SEQ ID NO: 1 or a protein having at least 90% identity to SEQ ID NO: 1) using only routine experimentation and would be capable of practicing the claimed invention without undue experimentation in view of instant claim amendment. Applicants argue the specification teaches techniques to crystallize and determine the conformational structure of an LTA4 hydrolase crystal and carry out screening method without undue experimentation. However, the instant claimed method is determined to require undue experimentation for the reasons below.

Applicants further argue instant specification disclose how to make and use any variants of at least 90% identity to the amino acid sequence of SEQ ID NO: 1 as disclosed in the Tables 5-7 on pages 20 to 23. However, being able to make and use variants having at least 90% identity to SEQ ID NO: 1 is irrelevant to the instant scope of enablement

rejection because the instant scope of enablement rejection is based on unpredictability to make and use the full scope of claimed method comprising crystallization of SEQ ID NO: 1 (or LTA<sub>4</sub> protein variant having at least 90% identity to SEQ ID NO: 1) under any condition by one skilled in the art. Also, it is unpredictable to make a crystal of LTA<sub>4</sub> protein variant having at least 90% identity to SEQ ID NO: 1 under the same crystallization condition described on page 36.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.'" (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a prima facie case are discussed below.

The breadth of the claims: Claims 60, 70, 80 and 83 (Claims 61-69, 70-79, 81-82 and 84-86 dependent therefrom) are so broad as to encompass a method of forming any protein crystals structure from a protein of SEQ ID NO: 1 (or a protein within at least 90% identity to SEQ ID NO: 1) in the presence of bestatin, with any unit cell dimensions and angles under widely varying any crystallization condition.

The nature of the invention: The invention is related to a method of crystallizing a protein of SEQ ID NO: 1 (or a protein having at least 90% identity to SEQ ID NO: 1) in the presence of bestatin, and methods of using structure coordinate of the protein crystal. At the time of the invention, methods of protein crystallization were well known in the art. However, the ability to crystallize a given protein was, at the least, challenging to a skilled artisan as even minor alterations in the conditions of crystallization could result in altered crystal forms, crystals of sub-diffraction quality, or a lack of crystal growth (as described in further detail below).

The state of the prior art: The level of one of ordinary skill; and The level of predictability in the art: Regarding the claimed crystals, the state of the art at the time of the invention acknowledges a high level of unpredictability for making the full scope of claimed crystals. For example, the reference of Branden et al. ("Introduction to Protein Structure Second Edition", Garland Publishing Inc., New York, 1999) teaches that "crystallization is usually quite difficult to achieve" (p. 375) and that "well ordered crystals...are difficult to grow because globular protein molecules are large, spherical, or ellipsoidal objects with irregular surfaces, and it is impossible to pack them into a crystal without forming large holes or channels between the individual molecules" (p.

374). Branden et al. further teaches that while there are instances where the structure of a protein has been resolved to a resolution of 1 Å, “only a few small proteins have been determined to such high resolution” (p. 382, first full paragraph). Also, Drenth et al. (“Principles of X-ray Crystallography,” Springer, New York, 1995) teaches that “the science of protein crystallization is an underdeveloped area” and “protein crystallization is mainly a trial-and-error procedure” (p. 1). One cannot predict a priori those conditions that will lead to the successful crystallization of a diffraction-quality crystal as evidenced by Kierzek et al. (2001, Biophys Chem 91:1-20), which teaches that “each protein crystallizes under a unique set of conditions that cannot be predicted from easily measurable physico-chemical properties” and that “crystallization conditions must be empirically established for each protein to be crystallized” (p. 2, left column, top). Even minor alterations in the crystallization parameters can affect crystallization as evidenced by Branden et al., which teaches that the formation of protein crystals is critically dependent on a number of different parameters, including pH, temperature, protein concentration, the nature of the solvent and precipitant, as well as the presence of added ions and ligands to the protein (page 375, middle). Branden et al. teaches that even small changes in the crystallization parameters, e.g., pH, can cause the molecules to pack in different ways to produce different crystal forms (page 374, bottom). Along these same lines, Wiencek (1999, Ann Rev Biomed Eng 1:505-534) teaches that “protein solubility will change dramatically as pH is altered by ~ 0.5 pH units...some systems are sensitive to pH changes as small as 0.1 pH units” (p. 514, bottom). In view of these teachings, a skilled artisan would recognize that it is highly unpredictable as to

whether diffraction-quality crystals of a protein of SEQ ID NO: 1 (or a protein having at least 90% sequence identity to SEQ ID NO: 1) can be achieved using the crystallization parameters as set forth at p. 36 of the specification or under any other set of crystallization condition(s). Alternatively, a skilled artisan would recognize that it is highly unpredictable as to whether diffraction-quality crystals of protein of SEQ ID NO: 1 (or a protein having at least 90% sequence identity to SEQ ID NO: 1) can be achieved using any crystallization parameters.

The amount of direction provided by the inventor; The existence of working examples: The specification discloses only a single working example of the claimed crystal and the method of crystallization thereof. See specification on page 36, lines 3-19. Other than this one working examples, the specification fails to provide guidance for altering the crystallization conditions for crystallizing protein of SEQ ID NO: 1 (or a protein having at least 90% sequence identity to SEQ ID NO: 1) with an expectation of obtaining diffraction-quality crystals. Further, the specification fails to provide guidance for soaking in any molecule into a crystal of SEQ ID NO: 1 (or a protein having at least 90% sequence identity to SEQ ID NO: 1) with any compound displacing the bestatin thereby forming a complex as disclosed on page 8 (Remarks received on 12/05/2007) with an expectation of obtaining diffraction-quality crystals.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of protein crystallization were known at the time of the invention, these methods are specific to a particular protein with two combinations of ligands as evidenced by the above teachings. Thus, a skilled artisan is

left to experiment by a trial and error process to determine whether the disclosed crystallization conditions can be applied to crystallization of SEQ ID NO: 1 (or any protein having at least 90% sequence identity compared to instant SEQ ID NO: 1) can be crystallized under a different set of crystallization parameters.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required to make all methods and crystals as broadly encompassed by the claims, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention.

Thus, applicant has not provided sufficient guidance to enable one skilled in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

***Conclusion***

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander D. Kim whose telephone number is (571) 272-5266. The examiner can normally be reached on 11AM-7:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Alexander D Kim/  
Examiner, Art Unit 1656

/Richard G Hutson, Ph.D./  
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